REMARKS/ARGUMENTS

Claims 1-22, 24, 25 and 27-32 are pending in the application.

Claims 1-20 and 29-32 have been withdrawn from further consideration as the result of an earlier restriction requirement.

In view of the examiner's earlier restriction requirement, applicant retains the right to present claims 1-20 and 29-32 in a divisional application.

Claims 22 and 27 have been amended.

In response to the Office Action of April 4, 2007, Applicant requests re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

***Elections/Restrictions***

The Election filed January 26, 2007 in response to the Office Action of December 27, 2006 has been acknowledged by the examiner. Claims 21-28 are currently under prosecution.

Applicant's election without traverse of Group IV, claims 21-28 in the paper filed January 26, 2007 has been acknowledged.

Applicant's election with traverse of the species of "cytotoxic moieties" has been acknowledged, and Applicant notes with appreciation that upon review and reconsideration, the

requirement for election of species, wherein the species all share a common utility, that is the treatment of a cancerous disease as disclosed by Applicant, has been withdrawn.

Applicant's request that Examiner consider the rejoinder of claims 29-32 to the elected group upon the finding of allowable material in the elected group has also been noted, and it is understood that upon a finding of allowable material, the request will be considered.

It is noted that the Examiner has set a priority date of March 26, 2004 for the instantly claimed and examined invention. The Examiner states that although a review of the parent application 10/713,642 reveals reference to Mab 5LAC-23 which is not deposited and the instant specification specifically teaches that Mab 5LAC-23 is deposited with the ATCC as PTA-5690, a review of the characteristics of the two antibodies reveals that the two antibodies are not the same. In particular, the Examiner indicates that a review of the instant specification reveals that PTA-5690 is found to bind to the SW620 colon cancer cell line but not to any of the other cell lines tested which include NCI- H460 and CCD-27sk. However, the Examiner goes on to indicate that a review of the 10/713,642 specification reveals on pgs 42-43 that Mab 5LAC-23 of that application was found to bind to both NCI-H460 and CCD-27sk.

Further, the Examiner points out that the instant specification specifically teaches that the ovarian cancer cell line OVCAR-3 was the only cancer cell line tested that was susceptible to the cytotoxic effects of purified 5LAC-23, wherein the tested cell lines included NCI-H460, CCd-27sk. However, (the Examiner state) a review of the 10/713,642 specification reveals that Mab 5LAC-23 of that application was cytotoxic to 8% of the NCI-H460 cells and 5% of the CCd-27sk cells. The Examiner then concludes that given the differences in functional characteristics of the two antibodies, both identified as Mab 5LAC-23, it would appear that the two antibodies are not the same and therefore the Examiner finds that there is no support in the parent application for the currently claimed invention and the priority date of March 26, 2004 for the instant invention has been assigned.

Attached hereto, the Examiner will find a declaration under 37 CFR 1.132 by David S. Young, which should obviate the issue regarding the priority date. It is respectfully requested that the Examiner reconsider the appropriate priority date in view of the declaration and provide priority to the earliest priority date claimed.

***Claim Rejections - 35 USC § 112***

Claims 21-28 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) are alleged to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art td which it pertains, or with which it is most nearly connected, to use the invention.

The Examiner states that:

> The claims are drawn to an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690 and to said PTA-5690 wherein the antibody is humanized, chimerized, conjugated to cytotoxic moieties, enzymes, radioactive compounds or hematogenous cells. It is noted that applicant specifically admits on the record, in the paper submitted January 26, 2007 that the species of claim 27 all share a common utility, that is the treatment of a cancerous disease as disclosed in the specification (see page 15 of the response). Further, the art recognizes that humanizing and chimerizing antibodies are drawn to processing of antibodies for use in *in vivo* treatment of disease. Thus, as inferred by the claims and contemplated in the specification, the claims are drawn to antibodies for therapeutic uses in the treatment of

cancerous disease and therefore read on therapeutic agents. Finally, as set forth below, the specification teaches that the claimed antibodies can be used for diagnosis, prognosis and prediction of therapy for cancerous diseases.

The specification teaches that this invention relates to the isolation and production of cancerous disease modifying antibodies (CDMAB) and to the use of these CDMAB in therapeutic and diagnostic processes, optionally in combination with one or more chemotherapeutic agents (para 0002 of the published application). The specification further teaches that each individual who presents with cancer is unique and has a cancer that is as different from other cancers as that person's identity. Despite this, current therapy treats all patients with the same type of cancer, at the same stage, in the same way. At least 30 percent of these patients will fail the first line therapy, thus leading to further rounds of treatment and the increased probability of treatment failure, metastases, and ultimately, death. A superior approach to treatment would be the customization of therapy for the particular individual. (para 0003 of the published application). In addition, with the advent of monoclonal antibodies, the possibility of developing methods for customized therapy became more realistic since each antibody can be directed to a single epitope. Furthermore, it is possible

to produce a combination of antibodies that are directed to the constellation of epitopes that uniquely define a particular individual's tumor (para 0004 of the published application). Thus, if a methodology was put forth which enabled the practitioner to treat each tumor independently of other patients in the same cohort, this would permit the unique approach of tailoring therapy to just that one person. Such a course of therapy would, ideally, increase the rate of cures, and produce better outcomes, thereby satisfying a long-felt need (para 0008 of the published application). The specification further teaches that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain,

ovarian, pancreatic, prostate and stomach cancers (para 0011 of the published application). In addition, the specification teaches that the application utilizes the method for producing patient specific anti-cancer antibodies as taught in the '357 patent for isolating hybridoma cell lines which encode for cancerous disease modifying monoclonal antibodies. These antibodies can be made specifically for one tumor and thus make possible the customization of cancer therapy. Within the context of this application, anti-cancer antibodies having either cell-killing (cytotoxic) or cell-growth inhibiting (cytostatic) properties will hereafter be referred to as cytotoxic. These antibodies can be used to treat tumor metastases (para 0024 of the published application). In addition, all the antibodies generated will be added to the library of anti-cancer antibodies since there is a possibility that other tumors can bear some of the same epitopes as the one that is being treated. The antibodies produced according to this method may be useful to treat cancerous disease in any number of patients who have cancers that bind to these antibodies. The PTA-5690 antibody was obtained after immunization of mice with cells from a patient's lung tumor (para 0026 of the published application). *In vitro* studies revealed that the antigen for the claimed antibody was detected on the SW620 colon cancer cell line and not on any of

the other cell lines tested and that purified antibody was found to be cytotoxic to the OVCAR-3 cell line (para 0025 of the published application). Furthermore, the specification teaches that the antigen to which the claimed antibody binds can serve as a target for therapeutic agents, and can also lead to prolonged survival of the treated mammal. Furthermore, this invention also teaches that detecting the antigen to which the claimed antibody binds in cancerous cells can be useful for the diagnosis, prediction of therapy, and prognosis of mammals bearing tumors that express this antigen (para 0030 of the published application).

One cannot extrapolate the teaching of the specification to the enablement of the claims because no evidence has been provided that the novel, lung tumor specific antibody produced by hybridoma PTA-5690 can target any tumor other than the patient specific lung tumor against which it was produced, that is, that it can be used in any of the (1) diagnosis, (2) treatment, (3) prognosis or (4) prediction of therapy for any tumors. In particular, the specification emphasizes the heterogeneity of individual cancerous tumors, stating that "each individual who presents with cancer is unique and has a cancer that is as different from other cancers as that person's identity. In agreement with this statement, the art recognizes,

as specifically drawn to antibody based therapeutics, that antigenic heterogeneity and insufficient target specificity are obstacles to clinical efficacy of antibody therapeutics, see Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) at p. 43. Further, Osband and Ross (Immunology Today, 1990, 11:193-195) teach that there is an obvious heterogeneity of tumors between patients and that the biochemistry and antigenicity of neoplastic cells show considerable variation (p. 194, para 2). Given this clearly defined problem, the specification teaches the advantages of customization of antibody therapy for a particular individual, that is the production of patient specific anti-cancer antibodies which encode for cancerous disease modifying monoclonal antibodies and states that this methodology would enable the practitioner to treat each tumor independently of other patients in the same cohort and would permit the unique approach of tailoring therapy to just one person. Although the specification hypothesizes that **there** is **a possibility** that other tumors can bear some of the same epitopes as the one that is being treated and that antibodies produced according to this method **may be useful** (emphasis added) to treat cancerous disease in any number of patients who have cancers that bind to these antibodies, given the known heterogeneity of cancerous tumors, it cannot be predicted whether or which

cancerous tumors would present with the epitope required for targeting by the claimed antibody. Although the specification hypothesizes that there is a possibility that other tumors bear some of the same epitopes, this is not sufficient to enable the use of this novel antibody for any of the diagnosis, treatment, prognosis or prediction of therapy of tumors as contemplated in the specification, in the absence of objective evidence that the epitope is in fact expressed on any primary tumors other than the lung tumor by which it was specifically stimulated. Clearly in the absence of expression, one would not know how to use the claimed antibody. Further, although the claimed antibody was produced against a specific lung tumor, there is no information in the specification drawn to assay of normal tissues in the patient from which the tumor was excised so that it could be determined whether or not the antigen to which the claimed antibody binds is differentially expressed even in that tumor compared to normal controls from the patient. As drawn specifically to the use of the cytotoxic properties of the claimed antibody as well as claims 22-23, 25-27, even if it were found that the antigen to which the claimed antibody binds is differentially expressed in tumors, other than the specific lung tumor which stimulated the production of the claimed antibody, compared to normal controls, it is well known that the art of

anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). In agreement with Gura and as drawn specifically to immunotherapy of cancers, the specification teaches, as set forth above, that in the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of

the published application). Further, Kaiser (Science, 2006, 313, 1370) specifically teaches that 90% of tumor drugs fail in patients; see col 3, 2nd to last para). Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would believe it more likely than not that the claimed method would function as inferred by the claims and as contemplated in the specification based only upon the demonstration that the claimed antibody binds to and is cytotoxic against a single cancer cell line in an *in vitro* setting. In particular because no evidence has been presented that the claimed antibody would be effective as an anticancer therapeutic. The fact that an antibody is cytotoxic in an *in vitro* system cannot be directly correlated to efficacy in an *in vivo* system. It is well known in the art that many of the factors known to limit human in *vivo* therapeutic efficacy of antibodies are lacking in *in vitro* model environments, for example, the *in vitro* system does not contain molecules that would be expected to proteolytically degrade the antibodies or that would activate an immunological response against the antibodies or that would nonspecifically absorb the antibodies in cells or tissues where the antibody has no effect. Further, it is clear that in the *in vitro* system exemplified,

the antibodies are in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure to the target site may be delayed or inadequate to insure an adequate concentration of the antibodies to be therapeutically effective. Those of skill in the art recognize that *in vitro* assays are useful to screen the effects of agents on cells. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared with the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a simple extrapolation of *in vitro* assays to therapeutic efficacy with any reasonable degree of predictability. In addition, those of ordinary skill in the art recognize that anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody and that variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by

degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Finally, the art recognizes the requirements for successful immunotargeting in cancer protocols as disclosed by White et al. (2001, Ann. Rev. Med., 2001, 52:125-145). In particular, White teaches that, for successful targeting and immunotherapy, besides specificity of the antibody for the antigen, other properties of the antigen should be considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether the antigens are shed, modulated or internalized influences the effectiveness of the administered immunotherapy (i.e. the antibody) (p. 126, second paragraph). Additionally, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126, paragraph before last). Thus, even if antigen which is bound by the

claimed antibody is expressed, differentially expressed, given that the specification does not provide any information drawn to the antigen expression it cannot be predicted if the antigen is present on a sufficient number of cancer cells, and in sufficient quantity, to allow for successful diagnostic or therapeutic targeting of cancer cells. In view of the above, one cannot predict whether the antigen is expressed in sufficient amount on cancer cells such that the claimed monoclonal antibodies would function as contemplated or inferred by the claims. Additionally, it cannot be predicted whether the antigen sheds, or is modulated, internalized, or down regulated in the primary cancer cells. Thus, again, it would require undue experimentation to determine if and under what circumstances the claimed monoclonal antibodies would be useful as contemplated and inferred by the claims.

Applicant is reminded that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior

art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." Given the lack of guidance in the specification, no one skilled in the art would believe it more likely than not that the claimed invention would function as contemplated or as inferred by the claims based only on the information in the specification and that known in the art at the time the invention was made. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claim by the claims or contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation is required in order to practice the claimed invention.

The above grounds have been given careful consideration. The claims have been modified to be exactly commensurate in wording and scope with those of U.S. 7,256,272, the parent case

of this application, which claims were allowed by the Examiner, directed toward a different disclose molecule, specifically the hybridoma cell line deposited with the ATCC having accession number PTA-4622.

It is respectfully submitted that the claims currently under examination, drawn to the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690; a humanized antibody produced from the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690, antigen binding fragments of the isolated monoclonal antibody and of the humanized antibody, and the claimed isolated monoclonal antibody, humanized antibody or antigen binding fragments thereof conjugated with a member selected from the group consisting of toxins, enzymes, radioactive compounds, and hematogenous cells, are fully enabled by the specification.

It is therefore respectfully submitted that the grounds of rejection are now obviated and this ground of rejection ought to be withdrawn.

Claims 23, 26, 27 further stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 26, 27 have been alleged to be indefinite because claims 23 and 26 recite the phrase "chimerized antibody". The exact meaning of the word chimera is not known. The Examiner indicates that the term chimera is generic to a class of antibodies, which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. Thus the metes and bounds of the claim protection sought allegedly cannot be determined.

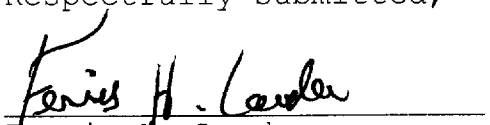
Accordingly, claims 23 and 26 have been cancelled and claim 27 has been amended, thereby obviating this ground of rejection, thereby obviating this ground of rejection.

Upon a recognition of allowable subject matter, it is respectfully requested that the Examiner contact the undersigned so that appropriate modifications to claims for which rejoinder has been requested can be expedited so as to allow the case to pass to issue with the rejoined claims.

SUMMARY

In light of the foregoing remarks and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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